PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/012095	25.10.2004	27.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D265/32

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No II Priority
- ☐ Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43*bis* 1(a)(i) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
- ☐ Box No VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/012095

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	10,12,13
	No:	Claims	1-9,11,14-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/012095

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: WO 01/62257 A2 (SEPRACOR INC) 30 August 2001 (2001-08-30)
d2: US-B1-6 323 368 (EVANS GRAHAM) 27 November 2001 (2001-11-27)
d3: WARD R S: "Dynamic Kinetic Resolution" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 6, no. 7, July 1995 (1995-07), pages 1475-1490, XP004048110 ISSN: 0957-4166

2-Novelty
The preparation of (+)-(2S,2S)-2-(3-chlorophenyl)-3,5,5-rimethyl-2-morphinol is disclosed in example 2 of d1. Present process differ from the method of d1 on account of the equivalents of L-DTTA used and on account of the final yield in (2S,3S) enantiomer.
D2 and d3 do not disclose any process for preparing the compound of present claim1. Hence, the requirements of Art. 33.2 PCT are met.

3- inventive step
3.1- D1 which discloses a process for preparing the morphinol of present claim 1 is regarded as the closest prior art.
The resolution process defined in claim 1 is carried out on a sample comprising the (-)-(2R, 3R) enantiomer of the morphinol derivative. Since the claim does not define a minimum amount of this enantiomer, said sample could even contain more than 50% of the other enantiomer. i.e. the (+)-(2S, 3S). Hence, the fact that at the end of the resolution the yield in the L-DTTA salt of the (+)-(2S, 3S) enantiomer is greater than 50% based on the initial sample, does not imply that a chemical conversion of the (-)-(2R, 3R) has taken place. For instance, if the starting mixture contains 2 moles of the (-)-(2R, 3R) and 8 moles of (+)-(2S, 3S) and at the end of the resolution 6 moles of (+)-(2S, 3S) are recovered, the yield would be of 60%. This yield would be achieved simply by a partial recovery of the (+)-(2S, 3S) enantiomer already present in the original mixture, without necessity of a chemical conversion of the (-)-(2R, 3R) enantiomer.
This means that the process of claim 1 cannot be regarded as a dynamic kinetic resolution (DKR), according to the definition given at page 3 of the description (lines 1 to 5), for these types of resolutions. The same conclusions can be drawn for the processes of claims 2 to 9, 11, 14-16.
These processes should more properly be regarded as resolutions which involve the

formation of diastereoisomeric salts and their selective precipitation.
Hence, the technical problem can be formulated as the provision of a further method for resolving the 2-(3-chlorophenyl)-3,5,5-trimethyl-2-morphinol.
Since the resolution of the 2-(3-chlorophenyl)-3,5,5-trimethyl-2-morphinol via formation of the diastereoisomeric salts with DTTA is already known from d1, it appears that the skilled person would arrive to the present process without any inventive skill.

3.2- The processes according to claims 10, 12 and 13 do involve a chemical conversion of the (-)-(2R, 3R) enantiomer to the (+)-(2S, 3S).
In respect to these claims, the thechnical problem can be formulated as the provision of a method for resolving the 2-(3-chlorophenyl)-3,5,5-trimethyl-2-morphinol which involves the conversion of the (2R,3R) enantiomer in the (2S, 3S).
D2 discloses (cf. example 1) the resolution of racemic tramadol through formation of diastereoisomeric salts with L-DTTA. The (-) enantiomer is obtained in 97% yield. The process involves at least two steps of salt formation and precipitation.
D3 discloses various methods of dynamic kinetic resolution. There is mention in this document for methods involving the use of L-DTTA.
Although, d2 discloses a method using L-DTTA which appears to involve the conversion of one enantiomer in the other one, it appears that there are no hints for applying such method to the resolution of 2-(3-chlorophenyl)-3,5,5-trimethyl-2-morphinol. Hence, the subject matter of claims 10,12 and 13 is considered to comply with the requirements of Art. 33.3 PCT.